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Phillips, Anna; Carroll, Douglas; Burns, Victoria; Drayson, Mark

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Neuroticism, Cortisol Reactivity, and Antibody Response to Vaccination.

Anna C. Phillips<sup>a</sup>, Douglas Carroll<sup>a</sup>, Victoria E. Burns<sup>a</sup>, and Mark Drayson<sup>b</sup>.

<sup>a</sup>School of Sport and Exercise Sciences, University of Birmingham, UK.

<sup>b</sup>School of Medicine, University of Birmingham, UK.

Address correspondence to: Anna C. Phillips, School of Sport & Exercise Sciences,  
University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK. Tel: 0044 121 414  
7510 Fax: 0044 121 414 4121 E-mail address: [A.C.Phillips@bham.ac.uk](mailto:A.C.Phillips@bham.ac.uk)

**Abstract**

This study examined whether neuroticism was related to the antibody response to influenza vaccination and whether the relationship was mediated by cortisol reactions to an acute laboratory mental stress. Antibody status was assessed at baseline and to a trivalent influenza vaccination in 57 students at five-weeks and five-month follow-up. Neuroticism was also measured at baseline. Cortisol was measured at rest and in response to a pressurised mental arithmetic task. At both follow-ups, higher neuroticism scores were associated with poorer A/Panama antibody response, following adjustment for baseline antibody titre. Higher neuroticism scores were also associated with blunted cortisol reactivity, and blunted cortisol reactivity was associated with poorer A/Panama antibody response, but only at five months. However, there was no conclusive evidence that cortisol reactivity mediated the association between neuroticism and antibody response.

**Descriptors:** Antibody Response, Cortisol Reactivity, Influenza Vaccination, Neuroticism

Assessing antibody response to vaccination is regarded as a useful model for studying psychosocial influences on *in vivo* immune function (Burns, Carroll, Ring, & Drayson, 2003; Cohen, Miller, & Rabin, 2001; Vedhara, Fox, & Wang, 1999). There is now considerable evidence linking frequent exposure to stressful life events and high levels of perceived stress with poorer antibody response to a variety of vaccinations (Burns et al., 2003; Cohen et al., 2001; Glaser, Kiecolt-Glaser, Malarkey, & Sheridan, 1998; Yang & Glaser, 2002). Far less attention, however, has been paid to the possible influence of key personality dimensions, such as neuroticism.

To date, only two vaccination studies have had personality as a primary focus. First, 12-year old girls who had not sero-converted prior to a live-attenuated rubella virus vaccination, and had lower antibody titres following vaccination, were characterised by higher internalizing or neuroticism scores and lower self-esteem at baseline (Morag, Morag, Reichenberg, Lerer, & Yirmiya, 1999). Similarly, a concept linked to neuroticism, trait negative affect, was negatively associated with antibody status following a second hepatitis vaccination in female graduates (Marsland, Cohen, Rabin, & Manuck, 2001). Given these preliminary results, it would seem worthwhile to examine further the association between neuroticism and response to vaccination.

Cortisol, an indicator of the activation of the hypothalamic-pituitary-adrenal axis, has long been considered a potential mediator of the relationship between psychosocial factors and immune response, although it is only recently that cortisol, and particularly cortisol reactions to acute stress, has been examined in the context of psychosocial factors and vaccination response. Elderly care-givers exhibiting a poor response to one strain of an influenza vaccine showed relatively higher daily salivary cortisol profiles, characterised as the area under the curve, than control participants (Vedhara, Cox et al., 1999). In contrast, in a more recent study, healthy adults characterised by lower antibody titres in response to a hepatitis B vaccination exhibited significantly smaller area under the curve cortisol profiles in response to an acute psychological stress task than individuals with relatively high antibody titres (Burns, Ring, Drayson, & Carroll, 2002). Finally, one research group found no association between cortisol response to naturalistic daily stressors and antibody status following influenza vaccination (Miller et al., 2004).

The role that cortisol reactivity might play in any association between neuroticism and antibody response to vaccination has yet to receive attention.

There is no consensus as to whether cortisol reactivity to acute stress is related to neuroticism. A number of studies have failed to show an association (Bohnen, Nicolson, Sulon, & Jolles, 1991; Kirschbaum et al., 1995; Miyabo, Asato, & Mizushima, 1979; Ockenfels et al., 1995; Roy, Kirschbaum, & Steptoe, 2001; Schommer, Kudielka, Hellhammer, & Kirschbaum, 1999; Singh, Petrides, Gold, Chrousos, & Deuster, 1999; Van Eck, Nicolson, Berkhof, & Sulon, 1996). However, neuroticism was positively related to cortisol reactivity to the stress of lecturing (Houtman & Bakker, 1991), and to the combined dexamethasone/corticotrophin-releasing hormone test (Zobel et al., 2004). In contrast, in a study using the same hypothalamic pituitary adrenal axis challenge, individuals with high neuroticism scores displayed significantly lower cortisol concentrations and change scores, and a tendency towards lower cortisol area under the curve than those with low neuroticism scores (McCleery & Goodwin, 2001).

The present study, then, examined the association between neuroticism and response to the trivalent influenza vaccine. In addition, cortisol was measured at rest and in response to an acute laboratory stress task. It was hypothesised that those with high neuroticism scores would show poorer antibody response to vaccination and that variations in cortisol reactivity would mediate this association.

## **Method**

### ***Participants***

Fifty-seven University of Birmingham students (31 men and 26 women) participated in the study. Mean age was 19.79 ( $SD = 2.25$ ) years and mean body mass index, based on reported height and weight, was 23.73 ( $SD = 3.21$ ) kg/m<sup>2</sup>. Eighty-eight percent described themselves as “white” and 95% reported being non-smokers. None of the participants had received an influenza vaccination or reported influenza in the past year, admitted to a history of negative reactions to blood sampling, or reported suffering from a current acute infection, chronic medical condition, or immune disorder. In addition, none had a history of vaccine-related allergies or side-effects, was pregnant or suspected to be pregnant, was breast-feeding, or was taking prescribed medication (excluding the contraceptive pill). They were paid £10 for participating and had a chance to win a further £50 from a

random draw. The study was approved by the appropriate Research Ethics Committees, and all participants provided written informed consent.

### ***Study Design***

The study comprised four sessions. In December / January, participants attended an initial session for 45 min, during which time they provided demographic information and completed a questionnaire assessing neuroticism. Stressful life events and perceived stress were also measured at this time point; the results are reported elsewhere (Phillips, Burns, Carroll, Ring, & Drayson, in press). At this time, a single venous blood sample was obtained. They were then medically screened for eligibility for a trivalent influenza vaccination. All were judged eligible and were duly vaccinated. Follow-up sessions took place five weeks and five months later. At each of the follow-up sessions, participants provided a further venous blood sample. From the three blood samples, antibody titres were determined for each of the three vaccine components. Between the five-week and five-month follow-ups, participants attended an individual two-hour laboratory session for acute psychological stress testing and cortisol measurement.

### ***Personality Questionnaires***

Neuroticism was measured by the Eysenck Personality Questionnaire (EPQ) neuroticism subscale (Eysenck & Eysenck, 1964). This measure comprises six Yes/No questions in which each “Yes” scores one point. Points are then summed to yield a total score. (Eysenck & Eysenck, 1964). The questionnaire has been used extensively with internal consistency and six-month test-retest reliability both greater than 0.70 (Hosokawa & Ohyama, 1993). The Cronbach’s  $\alpha$  for the current sample was .57. This might be regarded as somewhat low, but, as has been previously noted (Youngman, 1979), “Reliabilities for scales of an introspective nature do tend to be lower than those for object-directed (attitude) scales and...values around .6 are acceptable”, p.45.

### ***Salivary cortisol measurements***

During the laboratory session, which started at either 14:00 or 16:00 p.m., five stimulated saliva samples were obtained in 50ml tubes to determine free salivary cortisol at baseline and in response to the acute stress task. Samples were collected immediately preceding the stress task, immediately afterward, and then every ten minutes for the next 30 minutes. Before each sample, the participant was asked to swallow to dry the mouth and

then to gather as much saliva as they could for 1 minute. The participant then dribbled into the saliva collection tube, which was sealed. Samples were then centrifuged at 5000 rpm for 5 min, and subsequently frozen at  $-20^{\circ}\text{C}$  for analysis. Salivary cortisol samples were analyzed in duplicate by an enzyme-linked immunosorbent assay (ELISA) using a commercial kit (DRG Diagnostics).

### ***Blood samples, vaccinations and immunological assays***

At the initial and the two follow-up sessions, venous blood was collected from an antecubital vein into two 6 ml plain tubes (BD Vacutainer, Meylan Cedex) to assess antibody titre against each vaccine component. The blood samples were allowed to clot at room temperature for one hour, were centrifuged at 3500 rpm for 5 min and the separated serum was frozen at  $-20^{\circ}\text{C}$  until assayed for antibody titres. Following blood sampling in the initial session, participants received a Fluarix influenza vaccine (Glaxo SmithKline; Batch No: 18705B9) via intramuscular injection into the upper arm. The vaccine contained three viral strains: A/New Caledonia/20/99 (H1N1)-like strain - A/New Caledonia/20/99 (IVR-116); A/Moscow/10/99 (H3N2)-like strain - A/Panama/2007/99 (RESVIR-17); and B/Hong Kong/330/2001-like strain - B/Shangdong/7/97. The serum samples were analysed by the serology laboratory of Glaxo Smith Kline Beecham at Dresden, Germany. Anti-flu antibody titres were measured using a haemagglutination inhibition test as described in the World Health Organisation Manual on Animal Influenza Diagnosis and Surveillance (*World Health Organisation Global Influenza Programme: Manual on Animal Influenza Diagnosis and Surveillance*). The wild type flu strains, A/New Caledonia/20/99, A/Panama/2007/99, and B/Shangdong/7/97, were used for the antigenic analysis.

### ***Laboratory Stress Testing***

Participants were instructed not to eat, drink, and smoke for one hour prior to arrival at the laboratory. They were also asked to refrain from drinking coffee for two hours, and exercising and drinking alcohol for 12 hours before the session. The psychological stress task was the paced auditory serial addition test (Gronwall, 1977; Ring et al., 1999). Participants were presented with a series of single digit numbers and required, in each case, to add a number to the number presented next, saying the answer out loud. They also had to retain the last number heard in order to add it to the next one. Numbers were

delivered using an audio tape player. The 8-minute task consisted of four consecutive two minute periods of 50, 65, 75 and 100 digits at presentation rates of 2.4, 2.0, 1.6, and 1.2 seconds respectively. The experimenter sat 1 m distant from and adjacent to the participants and scored their answers. The task also involved elements of competition and social evaluation. A leader board was displayed prominently and participants informed that they should attempt to beat the five scores on the board. They were awarded 1000 points at the start of the task but lost five points for every addition they failed to compute correctly. Participants were videotaped and informed that the tapes would be assessed by “independent body language experts”; no such assessment was made. They were also instructed to watch themselves live on a television screen throughout the task. Finally, they received a brief burst of loud, aversive noise once during the first five of every ten trials, coincident with an error where one was made and at the end of the series of five if there were no errors. On arrival at the laboratory, participants had the procedure explained and were then allowed a practice of the mental arithmetic task. They were then exposed to three consecutive conditions: a 20-minute baseline rest period, the 8-minute stress task, and a 30-minute recovery rest period.

### ***Data Reduction and Analysis***

Antibody levels at baseline, five-week, and five-month follow-up were subjected to  $\log_{10}$  transformation. Cortisol reactivity was represented in two ways: first, as the difference between cortisol level 10 minutes post-task, when cortisol is most likely to peak (Kirschbaum, Strasburger, & Langkrar, 1993; Kirschbaum, Wust, Faig, & Hellhammer, 1992), and rest level; second, as the area under the curve described by the five sampling points. Comparisons of logged antibody titres and cortisol concentrations over time were undertaken using repeated measures ANOVA, using the Greenhouse-Geisser correction; partial  $\eta^2$  is reported to indicate effect size. The main analyses were by correlation and hierarchical regression. For regression, the dependent variables were logged antibody titre at the five-week and five-month follow-up, and to control for baseline antibody status, logged antibody titre at baseline was entered at step 1 into the initial models, with neuroticism or cortisol entered at step 2. Where significant associations emerged between antibody status and control variables (sex, age, body mass index), further hierarchical regression analyses were undertaken, again entering baseline logged



antibody titre at step 1, followed by the relevant control variables at step 2, with the key independent variables now being entered at step 3. This permitted determination of whether or not any associations between antibody status and the independent variables were the result of confounding. For mediation analysis, cortisol was entered at step 3, followed by neuroticism at step 4. Neuroticism data were available for 56 of the 57 participants, and cortisol reactivity and area under the curve data were available for 50 and 48 participants, respectively. Sufficient plasma for antibody analysis was provided by 56 participants at baseline, 55 at five-week, and 51 at five-month follow-up.

## **Results**

### ***Vaccination Response and Neuroticism***

The geometric mean (95%CI) antibody titre to each of the three vaccine strains (Phillips et al., in press) is displayed in Table 1. All participants responded with an initial increase in antibody titre from baseline at five weeks, which had declined to some extent by the five month measurement point, but remained above baseline levels.

For the sample as a whole, the mean (*SD*) score for neuroticism was 3.30 (1.57). There were no significant correlations between neuroticism and the baseline logged antibody titres for any of the three vaccine strains,  $r(55) = -.02$  to  $.10$ . Regression analysis of the antibody response to vaccination at five-week and five-month follow-up revealed significant negative associations between neuroticism and logged titre, adjusted for baseline logged titre, but only for the A/Panama viral strain. Individuals with higher neuroticism scores had lower antibody titres at both five weeks and five months,  $\beta = -.37$ ,  $t = 2.83$ ,  $p = .007$  and  $\beta = -.35$ ,  $t = 2.63$ ,  $p = .01$ , respectively (see Table 2). Of the control variables (sex, age, body mass index), only sex was associated with A/Panama antibody status; men had higher logged antibody titres than women at five weeks  $F(1, 53) = 4.46$ ,  $p = .04$ ,  $\eta^2 = .078$ , and five months,  $F(1, 49) = 4.35$ ,  $p = .04$ ,  $\eta^2 = .082$ . Consequently, sex was entered into the regression models at step 2. The associations between neuroticism and A/Panama antibody status were still statistically significant following adjustment for sex at both five-week,  $\beta = -.31$ ,  $t = 2.36$ ,  $p = .02$ , and five-month,  $\beta = -.31$ ,  $t = 2.33$ ,  $p = .02$ , follow-up (see Table 2).

### ***Cortisol Reactivity and Neuroticism***

Cortisol concentrations at each of the five time-points were subject to repeated measures ANOVA, using the Greenhouse-Geisser correction. There was significant variation in cortisol over time,  $F(4, 188) = 2.91, p = .04, \epsilon = .78, \eta^2 = .058$ . This was largely the result of a linear decline in cortisol,  $F(1,47) = 4.16, p < .05, \eta^2 = .081$ , although there was also a tendency for there to be a quadratic component in the temporal shift,  $F(1,47) = 2.99, p = .09, \eta^2 = .060$ . The summary data are presented in Figure 1. The increase in cortisol from baseline to 10 minutes post-task was not statistically significant,  $F(1, 49) = 0.02$ . Area under the curve was calculated using a version of the trapezoid (i.e. width  $\times$  ((height1 + height 2)  $\times$  0.5)) method, where width equals the difference in time in minutes between samples and height equals the concentration of cortisol at each time-point minus baseline. Subtracting baseline had the effect that negativity was preserved for values less than baseline, such that more positive area under the curve values indicated more reactive cortisol profiles and more negative values represented more of a linear decline from baseline. The four trapezoid values generated were summed to yield total area under the curve. The mean (*SD*) area under the curve was -0.46 (26.84) ng/ml/min. Area under the curve, calculated in this manner, was highly correlated with cortisol reactivity from baseline to 10 minutes post-task,  $r(46) = .92, p < .001$ . Neither cortisol reactivity nor area under the curve was associated with sex, age, or body mass index. However, neuroticism was negatively associated with cortisol reactivity,  $r(48) = -.31, p = .03$ , and area under the curve,  $r(46) = -.29, p = .04$ ; the higher the neuroticism, the smaller the cortisol reaction to acute stress and the smaller the area under the curve.

### ***Cortisol Reactivity and Antibody Status***

Whereas A/Panama antibody status at five weeks was not related to cortisol, antibody status at five months was related to both cortisol reactivity,  $\beta = .35, t = 2.57, p = .01$ , and area under the curve,  $\beta = .38, t = 2.81, p = .007$ ; following adjustment for baseline antibody titre, individuals with high cortisol reactions to acute stress exhibited better antibody responses to this vaccine strain.

### ***Possible Pathways of Association***

In order to test whether cortisol mediated the negative relationship between neuroticism and antibody status at five months, cortisol reactivity and area under the curve were entered at step 3, after baseline antibody titre at step 1 and sex at step 2, into separate

regression models predicting five-month A/Panama antibody status from neuroticism which was entered at step 4. For cortisol to mediate the relationship between neuroticism and five-month A/Panama antibody status, cortisol should not only be significantly associated with both variables, but upon entry into the model, should render the original neuroticism-antibody status association non-significant, while remaining itself a significant predictor of antibody status (Baron & Kenney, 1986). Adjusting for cortisol reactivity attenuated the association between neuroticism and antibody status at five months,  $\beta = -.23$ ,  $t = 1.64$ ,  $p = .11$ , but the association between cortisol reactivity and antibody status was also no longer significant,  $\beta = .24$ ,  $t = 1.70$ ,  $p = .10$ . Adjusting for area under the curve, however, not only rendered non-significant the association between neuroticism and antibody status,  $\beta = -.21$ ,  $t = 1.48$ ,  $p = .15$ , but in this model, the significant association between area under the curve and antibody status,  $\beta = .29$ ,  $t = 2.07$ ,  $p = .05$ , was preserved (see Figure 2). Nevertheless, the Goodman test (Goodman, 1960) revealed that the decrease in the association between neuroticism and A/Panama antibody status when including cortisol was not statistically significant,  $z = 1.56$ ,  $p = .12$ . Overall these analyses cannot be considered to provide conclusive evidence of a mediating role for cortisol area under the curve in the association between neuroticism and A/Panama antibody status.

## **Discussion**

Neuroticism was negatively associated with antibody response to the A/Panama viral strain of the trivalent influenza vaccination; the higher the neuroticism, the poorer the antibody response to vaccination. This finding is consistent with the outcomes of previous studies indicating that dispositional factors linked to neuroticism are related to vaccination response (Burns, Drayson, Ring, & Carroll, 2002; Glaser et al., 1992; Jabaa et al., 1996; Marsland et al., 2001; Morag et al., 1999; Snyder, Raghmann, & Sigal, 1990; Vedhara, Cox et al., 1999). However, as far as we are aware, this is the first demonstration that a stable personality trait is significantly related to both proximal and distal antibody response to vaccination.

In this data set, psychological stress was negatively associated with antibody response to the B/Shangdong viral strain, but not the A/Panama strain (Phillips et al., in press). This would suggest that personality variables affect the antibody response

independently of stress. It is difficult at this stage to determine why particular vaccine strains are sensitive to one sort of psychosocial influence but not another, although differences in strain novelty and participants' prior exposure to each viral strain have been cited previously to explain strain-specific associations (Vedhara, Cox et al., 1999). Further, the negative association between neuroticism and immunity observed in the present study resonates with the results from several studies examining other immune factors in this context, such as NK cell activity (Borella et al., 1999; Ishihara et al., 1999) and T cell count (Futerman, Wellisch, Zighelboim, Luna-Raines, & Weiner, 1996). It should be conceded, however, that the data available are not always consistent with this direction of association (Shea, Burton, & Girgis, 1993; Tjemmland, Soreide, Matre, & Malt, 1997), which may be a function of the immune outcome examined.

Cortisol reactivity to acute stress was also related to the antibody response to vaccination at five months, but the association was not in the expected direction; higher cortisol activity, whether measured as cortisol reactivity or area under the curve, was associated with a better A/Panama antibody response. This result contrasts with the findings of a previous influenza vaccination study, in which emotionally distressed carers had higher daily cortisol area under the curve profiles relative to less distressed controls (Vedhara, Cox et al., 1999). However, the direction of association found in the present study is not without precedent; lower cortisol area under the curve concentrations during and after acute laboratory stress were related to poorer antibody status following hepatitis B vaccination (Burns, Ring et al., 2002). Although cortisol reactivity in this study was negatively related to hepatitis B antibody status, the association did not survive adjustment for baseline cortisol. It is possible that exhibiting a lower or blunted cortisol response to acute stress reflects an underlying dysregulation of the hypothalamic pituitary adrenal axis which impacts negatively upon immune function. Recent research on wound healing, reveals that slower wound healing is also associated with blunted cortisol reactivity to the stress of receiving a punch biopsy (Engeland, Cacioppo, Bosch, & Marucha, 2003), and to standard laboratory stress tasks (J. Bosch, personal communication).

Studies where lower cortisol appears to be related to poorer immunity have, in the main, measured cortisol in the context of an acute stress task (Burns, Ring et al., 2002;

Buske-Kirschbaum et al., 1997; Engeland et al., 2003), whereas studies reporting that higher cortisol is related to a poorer immune outcome have measured daily basal cortisol levels (Vedhara, Cox et al., 1999) or cortisol profile following wakening (Ebrecht et al., 2004). Therefore, it seems plausible that high cortisol levels *per se* are detrimental to immunity, whereas high cortisol reactivity represents an adaptive response to acute stress, but blunted reactivity reflects underlying dysregulation of the hypothalamic pituitary adrenal axis, which is maladaptive for the control and best functioning of the immune system.

Neuroticism was negatively associated with the cortisol reactivity to acute stress, such that individuals with high neuroticism scores exhibited more blunted cortisol reactions. This adds weight to the contention that blunted cortisol reactivity is maladaptive. Negative associations between neuroticism and cortisol reactivity have been observed in response to the combined dexamethasone-CRH test (McCleery & Goodwin, 2001). In addition, parallel findings have emerged from the study of cardiovascular reactivity; individuals with high neuroticism scores exhibited blunted cardiovascular and catecholamine reactivity to stress (Burdick, Van Dyck, & Von Bargen, 1982; Forsman, 1980) and to the presentation of cardiotropic drug odour (Zverev & Mipando, 1999). However, it is important to note that counter evidence exists in which high neuroticism is related to high cortisol reactivity, although in one case, this finding did not quite achieve statistical significance (Houtman & Bakker, 1991), and in the other, this direction of effect was mainly due to a small subset of participants (Zobel et al., 2004). Further, other studies have failed to find an association between neuroticism and cortisol reactivity, although this could reflect restricted range of neuroticism scores (Schommer et al., 1999), low power (Kirschbaum et al., 1995), choice of stress task, or measurement of cortisol in plasma (Miyabo et al., 1979).

In the present study, we examined the possibility that cortisol reactivity may mediate the relationship between neuroticism and antibody response to influenza vaccination. A significant association between cortisol area under the curve and antibody response was evident for A/Panama only at five months. Further, the decrease in association between neuroticism and five-month antibody status following adjustment for cortisol area under the curve was not statistically significant. Nevertheless, the

hypothesis that cortisol hypo-reactivity arising from chronic and pervasive negative personality traits may be a pathway by which factors such as neuroticism are related to a poorer immune response following vaccine challenge is worth pursuing. In addition to its well known role in immune down-regulation to prevent over-activation or autoimmunity, one of the functions of cortisol in the body is to stimulate and permit the immune response to infection (Sapolsky, Romero, & Munck, 2000). However, studies in populations with more power to detect mediation are essential.

In summary, high neuroticism scores and blunted cortisol reactivity were related to a poorer antibody response to the A/Panama viral component of the influenza vaccination. This is the first study we know of to examine neuroticism and cortisol reactivity in the context of vaccination response. Further research using a variety of vaccinations and personality variables in different populations is needed to confirm that dispositional factors have a consistent and pervasive effect on *in vivo* measures of immune function.

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Table 1

*Geometric Mean (95% Confidence Intervals) Antibody Titres for each Viral Strain Pre-Vaccination and at the Five Week and Five-month Follow-ups*

Viral Strain	Pre-vaccination	Five-week Follow-up	Five-month Follow-up	ANOVA (p<.001)
A/Panama/2007/99	35 (3 – 437)	314 <sup>a</sup> (54 - 1820)	242 <sup>b</sup> (35 - 1698)	F(2,100) = 98.34, $\varepsilon = .57$ , $\eta^2 = 0.66$
A/New Caledonia/20/99	26 (1 – 477)	1928 <sup>a</sup> (182 - 20417)	1180 <sup>b</sup> (132 - 10715)	F(2,100) = 277.22, $\varepsilon = .63$ , $\eta^2 = 0.85$
B/Shangdong/7/97	17 (2 – 170)	377 <sup>a</sup> (40 - 3631)	161 <sup>b</sup> (11 - 2344)	F(2,100) = 276.6, $\varepsilon = .76$ , $\eta^2 = 0.85$

<sup>a</sup> significant difference between pre-vaccination and 5-week follow-up

<sup>b</sup> significant difference between pre-vaccination and 5-month follow-up

Table 2

*Hierarchical Regression Models for A/Panama Antibody Response at a) Five Weeks and b) Five Months Predicted by Neuroticism With and Without Adjustment for Sex.*

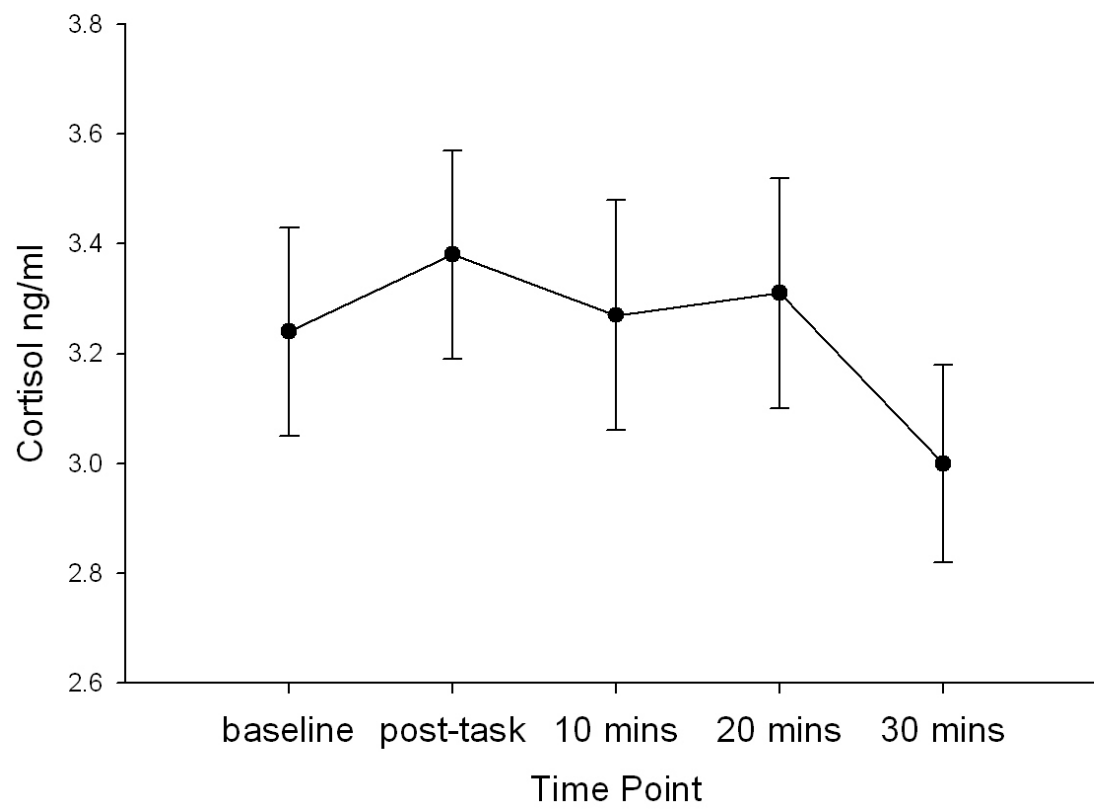
	$\beta$	$p$	$\Delta R^2$
a) Step 1 Baseline A/Panama	.03	.82	.001
Step 2 Baseline A/Panama	.05	.73	
Neuroticism	-.37	.007	.135
Step 1 Baseline A/Panama	.03	.82	.001
Step 2 Baseline A/Panama	-.01	.95	
Sex	-.30	.03	.086
Step 3 Baseline A/Panama	.01	.91	
Sex	-.21	.12	
Neuroticism	-.31	.02	.091
b) Step 1 Baseline A/Panama	.22	.13	.047
Step 2 Baseline A/Panama	.24	.08	
Neuroticism	-.35	.01	.122
Step 1 Baseline A/Panama	.22	.13	.047
Step 2 Baseline A/Panama	.18	.20	
Sex	-.27	.06	.072
Step 3 Baseline A/Panama	.21	.12	
Sex	-.21	.12	
Neuroticism	-.31	.02	.093

Figure 1

Cortisol concentration at baseline and in response to acute stress

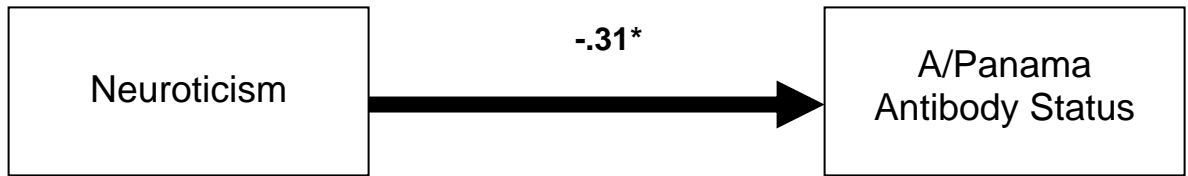
Figure 2

Mediation analysis of the association between neuroticism and five-month A/Panama antibody status by cortisol area under the curve: standardized regression coefficients are reported. In the original model (a) the association between neuroticism and antibody status was significant. However, it was no longer significant when cortisol area under the curve was entered: the significant association between cortisol and antibody status was preserved (b).

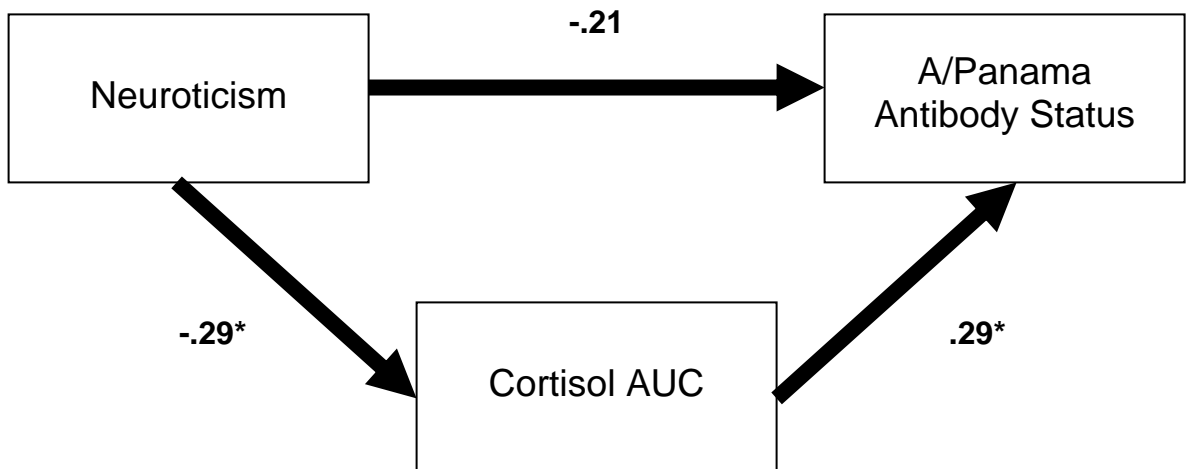




a)



b)



\*  $p < .05$